Original Research

Treatment Patterns in Patients With Newly Diagnosed Type 2 Diabetes in China: A Retrospective, Longitudinal Database Study

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ABSTRACT

Purpose: The objectives of this study were to examine the patterns of antihyperglycemic drug (AHD) therapy among patients with newly diagnosed type 2 diabetes mellitus (T2DM) in the general Chinese population, stratified by initial hemoglobin (Hb) A_{1c} level, and to assess whether treatment patterns are consistent with the recommendations published in the China Diabetes Society's clinical treatment guideline.

Methods: A retrospective database analysis was conducted, and data were obtained from the SuValue database. Prescribing patterns for diabetes treatments were determined from data obtained from the Nanhai District-based electronic medical records database, a subset of the SuValue database. Data from patients newly diagnosed with T2DM who also had at least 2 prescriptions for AHD medications after diagnosis and at least 1 HbA_{1c} test result during the 12 months prior to AHD treatment initiation, between January 1, 2004, and July 22, 2018, were included in the analysis. ANOVA, χ^2 test, and Kaplan-Meier survival analysis were used to examine differences between 4 initial-HbA_{1c} groups (<7%, 7%−<8%, 8%−<9%, and ≥9%).

Findings: A total of 4712 patients were included, with women accounting for 47.8%; the mean age (SD) of the study population was 56.44 (12.57) years. Men were more likely to have had a higher HbA_{1c} level at initial AHD treatment ($P < 0.0001$). The first-line therapies most frequently prescribed were metformin combination (29.5%), followed by insulin-including treatment (25.9%), and metformin monotherapy (19.2%). Metformin monotherapy (29.5%) was most commonly prescribed in patients with an HbA_{1c} level of <7%; metformin combination (31.7%), in patients with an HbA_{1c} level of 7%−<8%; and insulin-containing treatment, in patients with HbA_{1c} levels of 8%−<9% (28.1%) and ≥9% (38.4%). Insulin-including treatment was more commonly prescribed than was metformin combination in patients with an initial HbA_{1c} level of ≥8% after initial treatment. In third- and fourth-line treatments, patients with an HbA_{1c} level of ≥8% more prevalently were prescribed metformin combination and insulin-including treatment, while metformin combination and "other" treatment were more generally prescribed in patients with an HbA_{1c} level of ≤8%. However, 8.8% of patients with an HbA_{1c} level of <7% were prescribed insulin-including treatment as first-line therapy. In all lines of treatment, the percentages of patients prescribed insulin were increased with initial HbA_{1c} levels. A similar pattern was seen with dipeptidyl peptidase 4 inhibitors after first-line treatment. Overall, the median time to treatment switch was shorter than 3 months.

Implications: The findings from the present study depict a comprehensive overview of AHD-treatment patterns in patients stratified by HbA_{1c} level. The current treatment practices observed were inconsistent the published guideline, in terms of recommendations on metformin monotherapy and

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insulin use in first-line therapy. (*Clin Ther*. 2019;41:1440–1452)

Key words: China, diabetes mellitus, guidelines, treatment pattern.

INTRODUCTION

China has the largest population of people with diabetes in the world, with an estimated prevalence of 10.9% among the adult population[1] and the majority of cases being type 2 diabetes mellitus (T2DM). As estimated by the International Diabetes Federation, 13% of China's health expenditures (25 billion USD) is ascribed to diabetes.[2] In addition, poorly controlled hyperglycemia increases the risk for both microvascular and macrovascular diseases associated with T2DM, resulting in increasing social and economic burdens.[3] Hence, there is a need to understand the gap between treatment in clinical practice and the recommendations in treatment guidelines in order to enhance diabetes management.

Although diet and exercise are important T2DM-managment strategies, pharmacologic intervention is added in most patients for optimal glycemic control.[4] Currently, the primary medication treatments for diabetes are oral antidiabetic (OAD) drugs, insulin, and various combinations of these 2 therapies. According to the current guideline on the treatment of T2DM from the China Diabetes Society,[4] treatment should be tailored based on hemoglobin (Hb) A_{1c} level, which is used as both a diagnostic tool and a treatment goal. Metformin is recommended as the primary choice of initial treatment if the HbA_{1c} level is <7.0% (insulin therapy can be considered in patients with an HbA_{1c} level of ≥9.0%). In patients who fail to achieve the goal of glycemia control, dual therapy should be considered as the second step, followed by the addition of a third drug with a different mechanism of action. Insulin therapy should be considered only as a last step in the stepwise approach. The treatment guidelines on T2DM in China published from 2004 to 2018 are summarized in Table I.

Only 2 cross-sectional studies on the patterns of prescribing antihyperglycemic drug (AHD) regimens in patients with T2DM in clinical practice in China have been reported.[9,10] The DiaSTAGE (China Type 2 Diabetes Treatment Status Survey of Treatment Pattern of Oral Drug Users) study[9] reported that the most common OADs prescribed were insulin secretagogues (70.2%), without reference to HbA_{1c} level. The other study focused on the issue of treatment in patients of advanced age (>65 years-old), which showed that patterns of OAD prescribing were significantly different from those in patients aged <65 years.[10]

Although OAD treatment patterns were reported in those studies, data on the choice of AHD and switching patterns in patients with newly diagnosed T2DM are sparse. The objective of the present study was to document the treatment patterns in patients with newly diagnosed T2DM, based on initial HbA_{1c}, treatment changes during routine follow-up in clinical practice; and compliance with the T2DM treatment guideline.

MATERIALS AND METHODS

Study Design and Data Source

This retrospective, patient-level, longitudinal study used data from clinical practice, obtained from the SuValue database (Shanghai Suvalue Health Scientific Ltd, Shanghai, China). The database contains information on >90 million unique patients' medical records from 161 hospitals across 18 provinces in China. The database captures patient-encounter records on inpatient, outpatient, and emergency department visits, including demographics, diagnosis, laboratory measurements, prescriptions, procedures, and costs. The company partners directly with hospitals to extract data from their health information systems and then cleans, restructures, validates, and aggregates data from these different hospitals, and generates a structured patient-level longitudinal research database. The current study used a subset of data from the SuValue database, with the catchment of Nanhai district of Foshan City from January 1, 2004, to July 22, 2018, inclusive, including records from a total of 15 medical service institutions and 20 million encounters. All patients' records were linked with a unique identifier, and patients' personal identification information was deidentified and anonymized in this analysis. Authorization for database research was obtained when the database was integrated, so no ethics consideration or written informed patient consent was needed for this analysis.

Table I. Evolution of the guidelines on the treatment of type 2 diabetes mellitus in China.

Step	2004 Edition[5]	2008 Edition[6]	2010 Edition[7]	2013 Edition[8]	2017 Edition[4]
1	Biguanide/SU/glinide/AGI; consider metformin/pioglitazone/AGI in overweight patients	Metformin/TZD/SU/glinide/AGI; consider metformin in overweight patients	Metformin; alternatives are an insulin secretagogue or AGI if not contraindicated and if well tolerated	Metformin; insulin secretagogue or AGI should be considered in cases of contraindication or intolerance and insulin should be considered in patients with obvious hyperglycemia, ketosis, or ketoacidosis	Metformin; consider insulin secretagogues or AGI if no contraindications or intolerance, and consider insulin in patients with HbA_{1c} level $\geq$9.0%.
2	SU/glinide + pioglitazone/biguanide/AGI; consider metformin + glinide/AGI, or SU/glinide + biguanide/pioglitazone/AGI in overweight patients	+ Insulin; consider + TZD, SU/glinide, AGI in overweight patients	Insulin secretagogue/AGI; consider TZD or DPP-4i if well tolerated	Insulin secretagogue/AGI/TZD/DPP-4i	+ Insulin secretagogue/AGI/DDP-4i/TZD/SGLT-2i/insulin/GLP-1 RA
3	+ Insulin	+ Insulin in overweight patients	Basal insulin/premixed insulin, or insulin secretagogue/AGI/TZD/DPP-4i/GLP-1 RA	Basal insulin/premixed insulin, or insulin secretagogue/AGI/TZD/DPP-4i/GLP-1 RA	+ A third drug with a mechanism different from above
4	Insulin	—	Basal insulin + prandial insulin/premixed insulin analogue	Basal insulin + prandial insulin/premixed insulin analogue	+ Insulin

AGI = α-glucosidase inhibitor; DPP-4i = dipeptidyl peptidase-4 inhibitor; GLP-1 RA = glucagon-like peptide-1 receptor agonist; Hb = hemoglobin; SGLT-2i = sodium-glucose cotransporter 2 inhibitor; SU = sulfonylurea derivative; TZD = thiazolidinedione.

Study Population

Given the nature of the electronic medical records database for this diabetic population, the study applied a slightly modified 7-step algorithm[11] to identify patients with T2DM, as shown in Figure 1. The algorithm was based on a combination of diagnosis, medications, and patient characteristics. We decided to forgo step 7, which depended on whether body mass index measured closest to the time of diagnosis was $\geq$25 kg/m^2, since body mass index was not available from the database. We also lowered the age of starting insulin therapy without any prescription of other AHD regimens in step 1 from 35 to 30 years, in accordance with the Chinese treatment guideline,[4] to be more aligned with clinical practice. Step 1 excluded the prescription of metformin in identifying patients with T2DM, as this drug is also prescribed in patients with polycystic ovarian syndrome.[11] But metformin was included in the subsequent analysis after the patients with T2DM were identified.

In addition, eligible patients met the criterion that neither diabetes diagnosis nor the receipt of any AHD prescription occurred in the 6 months prior to the time of first diagnosis of diabetes, so that the population could be defined as newly diagnosed. Furthermore, eligible patients received at least 2 AHD prescriptions following the diagnosis and during the follow-up period. Finally, individuals were included in the study if they had >1 HbA_{1c} record in

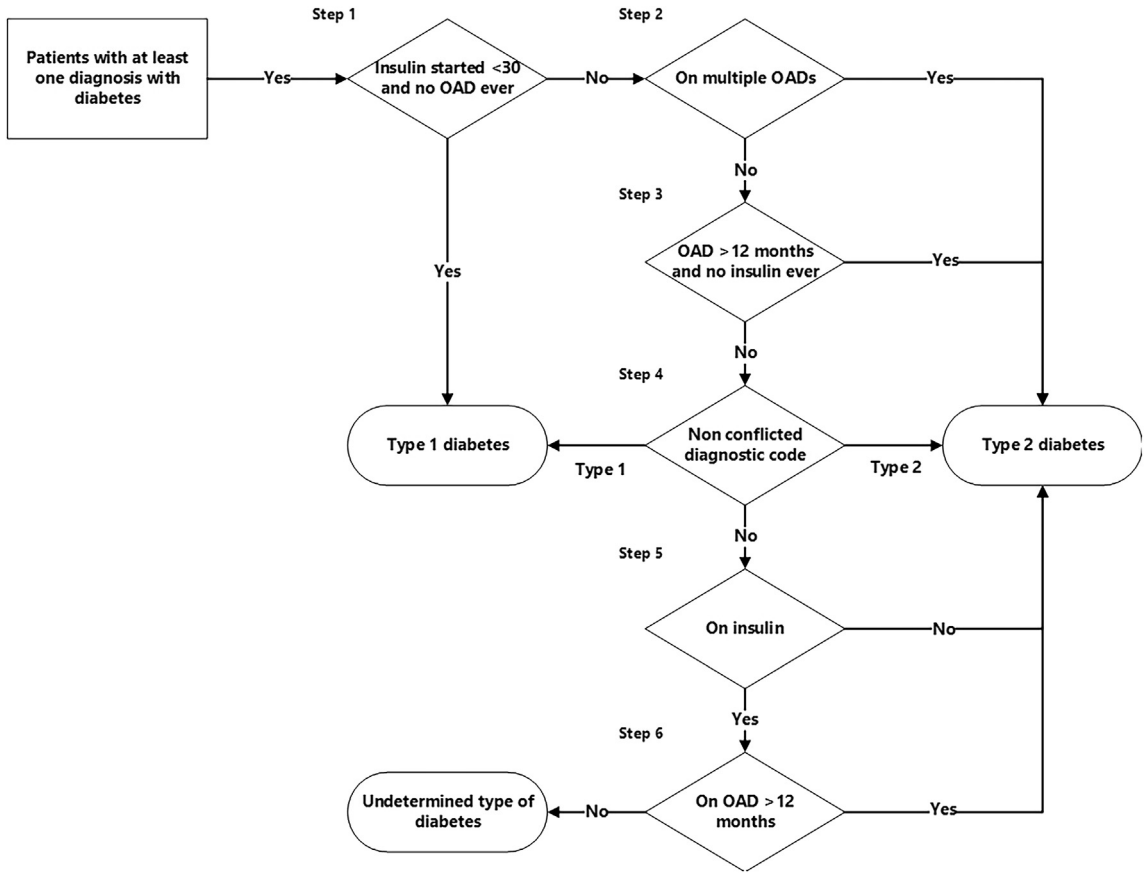

Figure 1. Modified algorithm for categorizing diabetes type in China. Step 1 excludes prescriptions for metformin. OAD = oral antidiabetic drug.

12 months prior to the time of the first prescription of AHD(s). The *index date* was determined as the date of the first prescription of AHD(s); 12 months prior to the index date was defined as the *baseline period*. The *follow-up period* began on the index date and ended on the earliest date of the following: end date of fourth-line treatment, date of the last data collection in the patient, or July 22, 2018.

Patients were excluded if they were diagnosed with type 1 diabetes, had an "undetermined" type of diabetes that was not identified by these steps, were pregnant during the baseline period, or had missing information on their date of birth or no baseline information. These attrition criteria resulted in a final sample of 4712 individuals, as detailed in Figure 2.

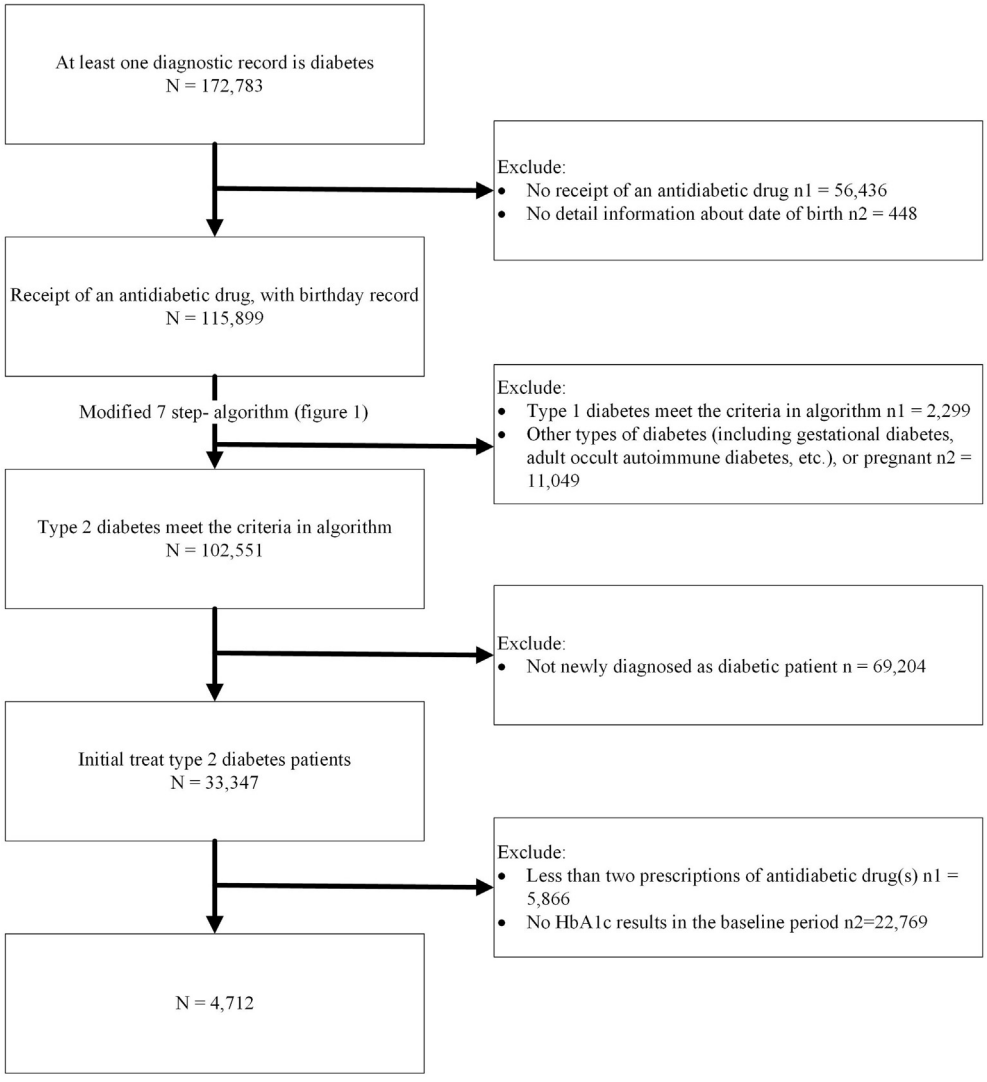

Figure 2. Disposition of the study patients with newly diagnosed type 2 diabetes mellitus in China. HbA_{1c}, hemoglobin A_{1c}.

Drug Classes and Aggregation

To characterize therapies for drug-utilization analysis, we sorted all AHDs into the following categories: metformin, sulfonylureas (SUs), dipeptidyl peptidase (DPP)-4 inhibitors, glucagon-like peptide 1 receptor agonists (GLP-1 RAs), insulin, α-glucosidase inhibitors (AGIs), meglitinide, sodium–glucose cotransporter (SGLT)-2 inhibitors, and "other" (eg, aldose reductase inhibitors, herbal extracts used as adjuvant therapy [Anatomical Therapeutic Chemical Classification (ATCC) class A10X]). All drugs were coded by the ATCC system.

After categorization of each drug by ATCC, there emerged 182 therapy patterns in total and 1862 clinical pathways when stratified by initial HbA_{1c} level. For the purposes of presentation, we further aggregated AHD treatment into the larger groups that applied to research on treatment patterns in T2DM across Europe[12]: (1) insulin-including treatment; (2) DPP-4 inhibitor–including treatment; (3) GLP-1-RA–including treatment; and (4) metformin combination treatment (ie, those containing metformin in <5% of patients). The remaining treatment regimens (eg, metformin, SUs, thiazolidinediones [TZDs], and "other" treatment) were shown separately if the percentage of patients was >5% of the study population; otherwise, they were lumped into the category of "other."

HbA_{1c} Measurement

Patients were categorized by level of glycemic control, as measured using HbA_{1c}, calculated as the mean of HbA_{1c} measurements obtained 3 months prior to the index date. Patients were stratified into 4 HbA1c groups: <7% (good glycemic control), 7%–<8%, 8%–<9%, and ≥9% (poor glycemic control). If a patient had only 1 HbA_{1c} result available from the 3 months prior to the index date, the initial HbA_{1c} level was used.

Switching and Censor

A *switch* was defined as a prescription being different from the previous prescription, such as a new class of AHD replacing the previous one. The first prescription was the *first-line therapy* and was considered as switched to the next line, *second-line treatment,* if a drug regimen had any modifications. Patients were censored at the date of the end of follow-up.

Statistical Analysis

Patients were categorized based on HbA_{1c} level prior to the index date. Percentages of patients prescribed specific ATCC-classified AHDs or treatment aggregations were summarized by baseline HbA_{1c} level and according to the step of treatment. We used ANOVA for continuous variables and the χ^2 test for categorical variables to examine differences between groups. The Mann-Whitney *U* test was performed to compare age differences by sex. The *median time to switch* to the next treatment, or censor, whichever came first, was estimated using Kaplan-Meier survival analysis. *P* values from 2-sided tests were deemed to be statistically significant at <0.05. All data were analyzed using Python software version 3.7.0 (Python Software Foundation, www.python.org) and R Statistical Package version 3.4.4 (R Foundation, Vienna, Austria).

RESULTS

Demographics, Comorbidities, Medical Insurance

A total of 4712 patients newly diagnosed with T2DM were included in this analysis. Of these, the initial HbA_{1c} level was <7% in 1259 patients, 7%–<8% in 788, 8%–<9% in 570, and ≥9% in 2095 (Table II). The mean (SD) age of the overall population was 56.44 (12.57) years, with 47.8% being women. The mean age was observed to be higher in the group with HbA_{1c} <7% versus 8%–<9% and versus ≥9% (58.27 vs 55.36 and 55.40, respectively; both, $P < 0.05$). The age and sex distributions are shown in Figure 3. The mean ages were significantly different between men and women (54.69 vs 58.35; $P < 0.0001$). The sex distribution was varied in the 4 groups ($P < 0.001$) (Table II).

About three fourths of the patients had medical insurance. There were no significant differences in the prevalences of clinical characteristics between the 4 groups, except hypertension and dyslipidemia. Hypertension was the most common comorbidity (18.8%), followed by stroke (4.8%), coronary heart disease (3.7%), and dyslipidemia (3.4%). A significant percentage of patients with HbA_{1c} <7% had hypertension (23.9%; $P < 0.0001$) (Table II).

Drug Utilization Without Drug Aggregation

OAD monotherapy was the most frequently prescribed treatment in all lines of AHD treatment,

Table II. Characteristics of patients with newly diagnosed type 2 diabetes mellitus in China, by glycosylated hemoglobin (HbA_{1c}) level. Data are given as numbers (%) of patients unless otherwise noted.

Characteristic	All Patients (N = 4712)	HbA_{1c} Level				*P**
		<7% (n = 1259)	7–<8% (n = 788)	8–<9% (n = 570)	≥9% (n = 2095)	
Age						
Mean (SD), y	56.44 (12.57)	58.27 (12.54)	57.04 (12.63)	55.36 (12.59)	55.40 (12.42)	<0.0001†
≥60 y	1979 (42.0)	615 (48.8)	351 (44.5)	210 (36.8)	803 (38.3)	<0.0001
Sex						<0.0001
Male	2458 (52.2)	584 (46.4)	392 (49.7)	303 (53.2)	1179 (56.3)	
Female	2254 (47.8)	675 (53.6)	396 (50.3)	267 (46.8)	916 (43.7)	
Payer type						<0.0001
Social health insurance	3489 (74.0)	1015 (80.6)	598 (75.9)	460 (71.2)	1470 (70.2)	
Self-pay	1223 (26.0)	244 (19.4)	19 0 (24.1)	164 (28.8)	625 (29.8)	
Comorbidities						
Hypertension	885 (18.8)	301 (23.9)	157 (19.9)	88 (15.4)	339 (16.2)	<0.0001
Stroke	225 (4.8)	70 (5.6)	35 (4.4)	22 (3.9)	98 (4.7)	0.393
Coronary heart disease	174 (3.7)	55 (4.4)	32 (4.1)	16 (2.8)	71 (3.4)	0.294
Dyslipidemia	158 (3.4)	76 (6.0)	23 (2.9)	15 (2.6)	44 (2.1)	<0.0001
Obstructive sleep apnea/agrypnia	66 (1.4)	28 (2.2)	13 (1.6)	3 (0.5)	22 (1.1)	0.010
Atrial fibrillation	41 (0.9)	10 (0.8)	10 (1.3)	2 (0.4)	19 (0.9)	0.347
Congestive heart failure	25 (0.5)	8 (0.6)	4 (0.5)	2 (0.4)	11 (0.5)	0.939

* Statistical difference between the 4 HbA_{1c} subgroups, as calculated by 1-way ANOVA or by χ^2 test.
† Statistically significant differences ($P < 0.05$) between subgroups HbA_{1c} <7% and HbA_{1c} 7%–<8%; HbA_{1c} <7% and HbA_{1c} 8%–<9%; HbA_{1c} <7% and $HbA_{1c} \geq 9\%$; and HbA_{1c} 7%–<8% and $HbA_{1c} \geq 9\%$ (Bonferroni test after ANOVA).

ranging by HbA_{1c} category from 35.9% to 37.9%, followed by OAD dual therapy, insulin monotherapy or combined with an OAD(s), and OAD triple therapy (Table III). OAD dual therapy was mainly used in the second line of treatment (35.7%), whereas OAD monotherapy was mainly used in the first line of treatment (37.9%). The category of >3 OADs was seldom used in any line of treatment (≤1.3%) (Table III).

In terms of drug utilization in first-line treatment, the most commonly used medication was metformin, at 58.5% (lowest) and 72.3% (highest) among patients with HbA_{1c} <7% and $HbA_{1c} \geq 9\%$, respectively (Table IV). The most discernible pattern was the prescribing of insulin in tandem with HbA_{1c} level; insulin prescribing was increased from 9.5% (HbA_{1c} <7%) to 42.5% ($HbA_{1c} \geq 9\%$). A similar trend was seen in the prescribing of DPP-4 monotherapy or in combination (1.8%–5.7%) (Table IV).

Treatment Patterns After Drug Class Aggregation

With regard to treatment patterns after drug aggregation, Figure 4 illustrates the diversity of treatment patterns observed across different initial HbA_{1c} levels. In first-line treatment, metformin-containing treatment was the most prevalent pattern, accounting for 29.5% (metformin combination, 10.2%; metformin + SU, 13.9%; and metformin + AGI, 5.3%). Insulin-including treatment and metformin monotherapy ranked second and third, accounting for 25.9% and 19.2%, respectively. Regarding the different HbA_{1c} levels, metformin monotherapy (29.5%) was prescribed most commonly in HbA_{1c} group <7%, followed by AGIs (14.6%) and SUs (12.7%). Insulin-including treatment was most prevalently prescribed in HbA_{1c} groups 8%–<9% and ≥9% (28.1% and 38.4%, respectively). The percentages of metformin and SU

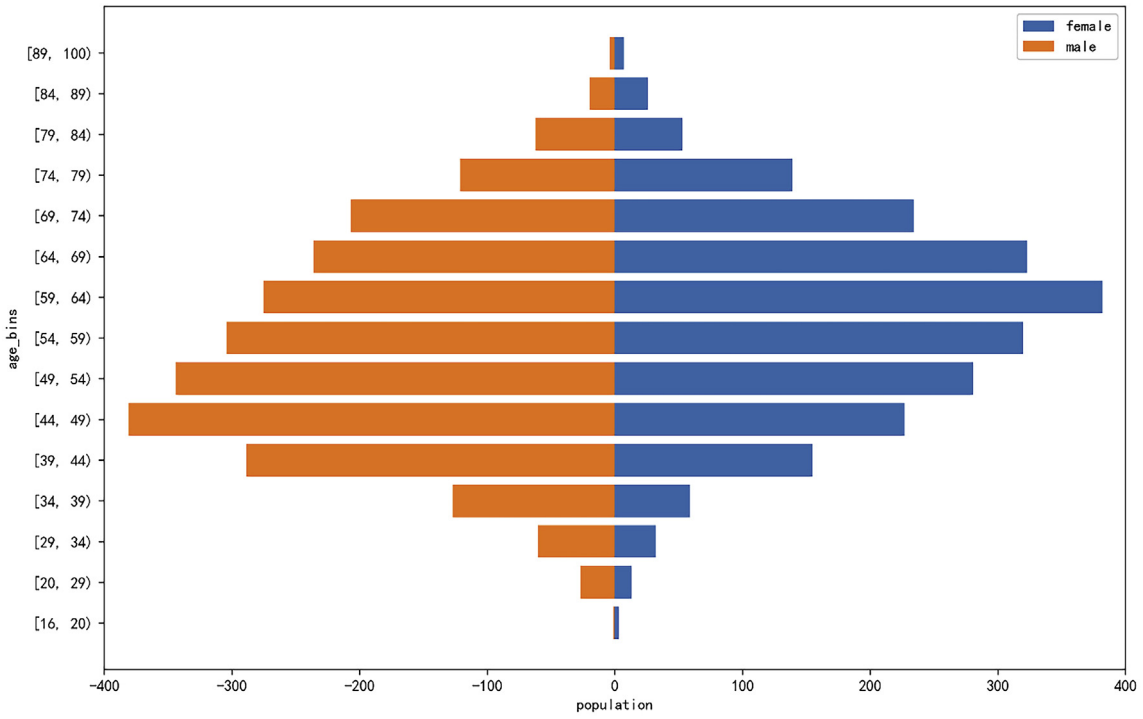

Figure 3. Age and sex profiles in patients with newly diagnosed type 2 diabetes mellitus in China. An HbA1c level: group 1, <7%; group 2, 7%−<8%; group 3, 8%−<9%; group 4, ≥9%.

prescribing as monotherapy were diminished with increased HbA_{1c}. On the other hand, prescribing of insulin monotherapy or in combination trended in the opposite direction in all lines of treatment (Figure 4).

For the choice of treatment in the second line, some patients were prescribed metformin combination therapy (12.6%). In the groups with HbA_{1c} 8%−<9% and ≥9%, second-line therapy often consisted of metformin combination (35.4% and 29.8%,

Table III. Patterns of treatment in patients with newly diagnosed type 2 diabetes mellitus in China, by line of treatment. Data are given as numbers (%) of patients.

Treatment	First Line (n = 4712)	Second Line (N = 3436)	Third Line (N = 2392)	Fourth Line (N = 1782)
1 OAD category	1785 (37.9)	1246 (36.3)	863 (36.1)	640 (35.9)
2 OAD categories	1372 (29.1)	1227 (35.7)	818 (34.2)	606 (34.0)
3 OAD categories	315 (6.7)	394 (11.5)	270 (11.3)	209 (11.7)
>3 OAD categories	21 (0.4)	28 (0.8)	25 (1.0)	23 (1.3)
OAD(s) + insulin/insulin alone*	1219 (25.9)	541 (15.7)	416 (17.4)	304 (17.1)

OAD = oral antidiabetic drug.
* Drug regimens that included insulin are deemed OAD(s) + insulin/insulin alone.

Table IV. Percentages of each drug class used in first-line treatment, without drug aggregation, by concentration of hemoglobin (Hb) A_{1c} subclass.*

Drug	HbA_{1c} Level			
	<7% (n = 1259)	7–<8% (n = 788)	8–<9% (n = 570)	≥9% (n = 2095)
Metformin	58.5	69.3	68.8	72.3
Sulfonylurea	30.2	34.3	39.1	39.0
α-Glucosidase inhibitor	27.6	27.0	29.5	35.5
Glinide	9.8	13.8	16.8	12.9
Insulin	9.5	20.1	30.5	42.5
Thiazolidinediones	5.6	8.9	8.4	8.0
DPP-4 inhibitor	1.8	2.0	3.7	5.7
Other drug related to diabetes treatment	3.9	6.2	9.8	12.9

* Percentages add to >100% due to treatment with individual drugs without aggregation.

respectively). In terms of third- and fourth-line therapy, metformin combination and insulin-including therapy were prescribed among the patients with higher initial HbA_{1c} levels, while patients with lower initial HbA_{1c} levels were more frequently prescribed "other" treatment, which aggregated groups of treatments, and metformin combination. The censored population was commonly seen in treatment subsequent to the first line. Patients with poor initial glycemic control were more often prescribed insulin-containing treatment during the study period. A similar pattern was seen with DPP-4 inhibitors after

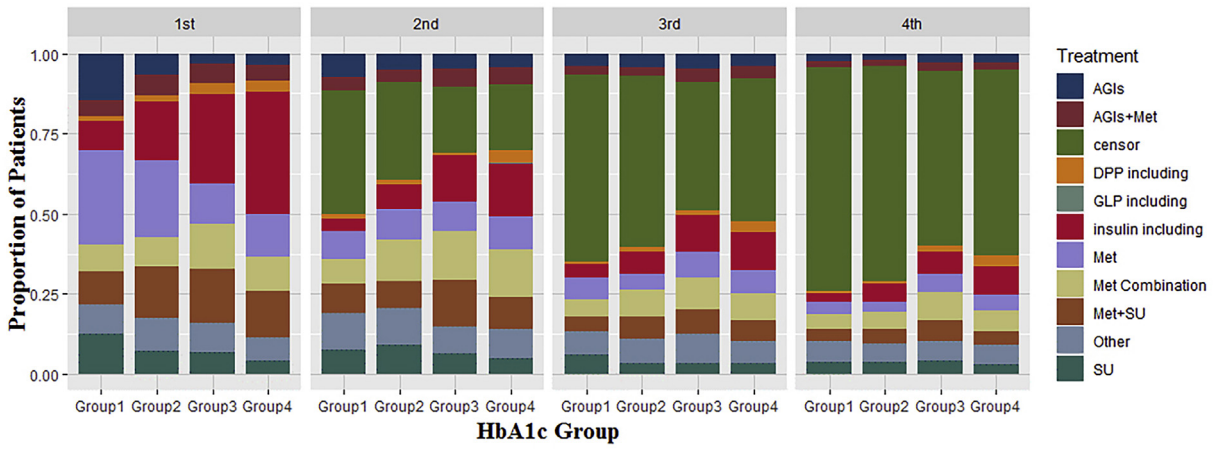

Figure 4. Treatment switches in each line of treatment during the study period in patients with newly diagnosed type 2 diabetes mellitus in China. An HbA1c level: group 1, <7%; group 2, 7%–<8%; group 3, 8%–<9%; group 4, ≥9%. AGI = α-glucosidase inhibitor; DPP including = regimen including a dipeptidyl peptidase 4 inhibitor; GLP including = regimen including glucagon-like peptide 1 receptor agonist; Met = metformin; SU = sulfonylurea derivative.

the first line. However, the most prominent pattern was found with GLP-1-RAs—including treatment, with only 2 patients prescribed this treatment in the second line (Figure 4). Combination treatment with metformin, which included metformin + AGI, metformin + SU, and metformin + "other" AHD(s), was most commonly prescribed in all groups (Figure 4).

Time to Treatment Switch

Overall, the median persistence time between treatment lines was shorter than 3 months. The time periods between treatment step-ups differed by initial HbA_{1c} level and was more prolonged at the first-line treatment. The median time between first- and second-line treatments in the group with HbA_{1c} <7% was 75 days (95% CI, 61−88) and in $HbA_{1c} \geq 9\%$ was merely 25 days (95% CI, 22−27) (Figure 5). Persistence durations between therapies were significantly different between initial-HbA_{1c} groups (Figure 5).

DISCUSSION

This research used a database to profile treatment patterns in clinical practice according to initial HbA_{1c} level and assessed compliance with the current guideline on the treatment of T2DM in China.[4] The findings will increase the understanding of treatment patterns of different steps in the clinical practice setting as well as how treatment patterns change over time.

A key strength of this study was that it applied initial HbA_{1c} level—as the guideline recommends for determining blood glucose control in diabetes—calculated as the mean measurement of HbA_{1c} over the preceding 2 or 3 months, in the assessment of whether treatment practices are consistent with the guideline recommendations.

At the time of receipt of the first-line treatment, women comprised in the majority (53.6%) of patients with an HbA_{1c} level <7%, which translated to good glycemic control, but composed the minority (43.7%) of patients with an HbA_{1c} level ≥9%, which translated to poor glycemic control. This finding reflects that men may be more likely to delay treatment than women, as reported previously.[13,14] In addition, the age in men at first diagnosis of T2DM was younger, possibly reflecting that men in the Nanhai District were exposed to more risk factors, such as high daily alcohol consumption or smoking,

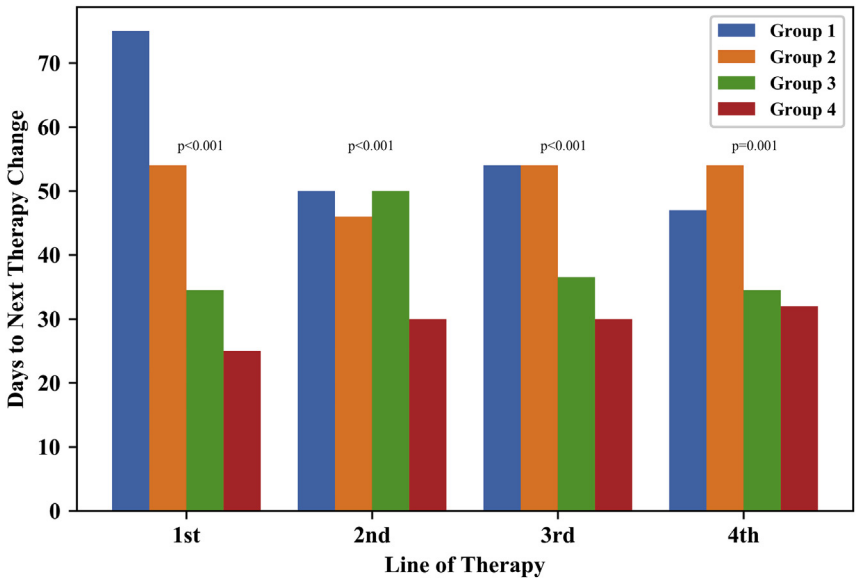

Figure 5. Median times to switching to sequential treatments during the study period in patients with newly diagnosed type 2 diabetes mellitus in China. An HbA1c level: group 1, <7%; group 2, 7%−<8%; group 3, 8%−<9%; group 4, ≥9%.

compared with women. Other research has also indicated that diabetes is more frequently diagnosed at a younger age in men due to sex differences in both biological and psychosocial factors.[15] However, further research should be conducted to explore why men tended to have worse glycemic control as well as whether the treatment guideline should be sex specific.

We also found that patients with poor glycemic control ($HbA_{1c} \geq 9\%$) were significantly younger on average. This finding is consistent with those from previous studies. One study reported that younger age was significantly linked with worse glycemic control.[16] Another study documented that patients <65 years of age had poorer glycemic control compared to their older counterparts.[17] Presumably, elderly patients were more adherent to diet therapy, while young patients may have had irregular work schedules or other stresses before the initiation of drug therapy. Notably, the rate of dyslipidemia in the group with poor glycemic control ($HbA_{1c} \geq 9\%$) was lower, which may have been related their younger age, as previous research has reported.[18] In young men, medical education and management by HbA_{1c} monitoring are necessary for determining hyperglycemic status and comorbidities.

As for drug utilization without drug aggregation, about one third of patients were started on treatment of diabetes with 1 OAD, and this rate was decreased slightly over the study period. The treatment pattern for OAD monotherapy as the primary therapy in patients with newly diagnosed T2DM was similar to that in previous studies.[19,20]

As for treatment patterns after drug aggregation, we noted that, consistent with the guideline,[4] metformin monotherapy or in combination or insulin secretagogues were most commonly prescribed in the initial treatment step. However, only 19.2% were prescribed metformin monotherapy, while 29.5% were prescribed metformin in combination with "other" OAD(s), and 25.9% of patients were prescribed insulin-including treatment—despite the fact that the Chinese guideline began recommending metformin as first-line treatment in the 2004 version.[5] This finding contrasts with those from other countries, where metformin monotherapy has played the dominant role in initial therapy, accounting for 65%–90%.[12,18,21] Meanwhile, the prescribing of insulin in first-line therapy was unreasonably high (8.8%) in patients with good glycemic control (initial HbA_{1c} level <7%), which was inconsistent with the recommendation in the most recent Chinese treatment guideline.[4] There is also no compelling rationale for initiating drug therapy with insulin when the HbA_{1c} is marginally high, as insulin use has been associated with notable unwanted effects, such as weight gain and hypoglycemia. Furthermore, the new drugs, such as the DPP-4 inhibitors and GLP-1 RAs, were not often used in clinical practice in China. These AHDs have the demonstrated benefits in decreasing the risk for hypoglycemia, and blood pressure neutrality and reduction, and have been recommended for use in treatment intensifications in second- and third-line therapies. Although data from a long-range time period, from 2004 to 2018, were included, the patients included were mainly (90%) distributed in 2012 and after. The guideline changed from 2004 to 2018, and the medications recommended in first-line therapy were slightly changed in the 2010 edition. Treatment patterns may be affected by changes in the guideline, as the influence of conventional treatment in clinical practice, or clinical inertia, would be continued over time.

The median time to treatment switch differed between the HbA_{1c} groups. A short time to switch following therapy initiation, especially in patients with an initial HbA_{1c} level of ≥9%, may imply that patients are receiving more intensive therapy or are more actively managing their glycemic levels. However, it may also imply that patients are in poor tolerance of this treatment. A longer time to switch may imply inertia when proper therapy switches need to occur, or patients may be in good glycemic control after treatment. Because routine HbA_{1c} results were not available, it was outside of the scope of the present study to assess the factors affecting the times to switching to subsequent lines.

The findings from the present study also suggest that patients with poor glycemic control at the initial treatment saw shorter median times to treatment switches in the follow-up treatments. As expected, when initial HbA_{1c} level was ≥9%, the mean median time to treatment switch was <1 month (29.3 days), while when initial HbA_{1c} level was <7%, the mean median time was ~2 months (56.5 days). In addition, the results also reveal that the prescribing of insulin was greater with increased initial HbA_{1c} level in all lines. This finding is somewhat consistent with

previous studies that have shown that early use of insulin-including treatment can significantly improve glycemic control and be a "bridge" from oral-only to insulin-only therapy.[22]

In our study, SGLT-2 inhibitors and GLP-1 RAs were rarely prescribed in the patient samples, although they were recommended in second or later lines of antihyperglycemic treatment, especially in overweight patients. The reason that we did not observe these classes of drug is largely because the first SGLT-2 inhibitor was approved only recently in China, in 2017. DPP-4 inhibitors were more broadly used in clinical practice, as a long-term outcomes study showed that this drug class of has no negative impact in terms of weight gain.[23,24]

There were limitations in our study. Because HbA_{1c} data were not routinely available from Chinese clinical practice, we could not directly evaluate the effectiveness of different classes of AHD medication in glycemic control. Hence, an intensive analysis of data after the first line of treatment was not possible. It is important to note that the Chinese guideline on the treatment of T2DM changed during the study period, and therefore we could not determine the impact of the guideline changes on treatment patterns.[4–8] Our study included data from 15 hospitals in the Nanhai District of Foshan, and the results may not be representative of AHD treatment patterns in the whole country. Caution should be exercised in generalizing the results to other populations.

CONCLUSIONS

Although the updated guideline on the treatment of T2DM in China promotes the use of metformin monotherapy in patients initiating AHD treatment, this research found that treatment was consistent with guideline recommendations in only about one fifth of patients (19.2%), while insulin prescribing accounted for 25.9% of drugs used in first-line treatment. Meanwhile, insulin was unreasonably used (8.8%) in patients with an HbA_{1c} level of <7%. The results also suggest that men were more likely to have poor glycemic control, and that younger age was related to poor glycemic control at the time of receipt of the first AHD medication. Furthermore, newer treatments (SGLT-2 inhibitors and GLP-1 RAs) had not found a place in treatment practice during the study period. The results are of significance to clinical decision makers, policymakers, and other health care professionals because they contain key information on the gap between treatment practice and the guideline, as well as information on the diverse clinical pathways in the treatment of T2DM in the Chinese population.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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